ΕΛΛΗΝΙΚΗ ΟΥΡΟΛΟΓΙΚΗ ΕΤΑΙΡΕΙΑ (Ε.Ο.Ε.)

14η Εκπαιδευτική Εβδομάδα
Ελλήνων Ειδικευομένων Ουρολόγων

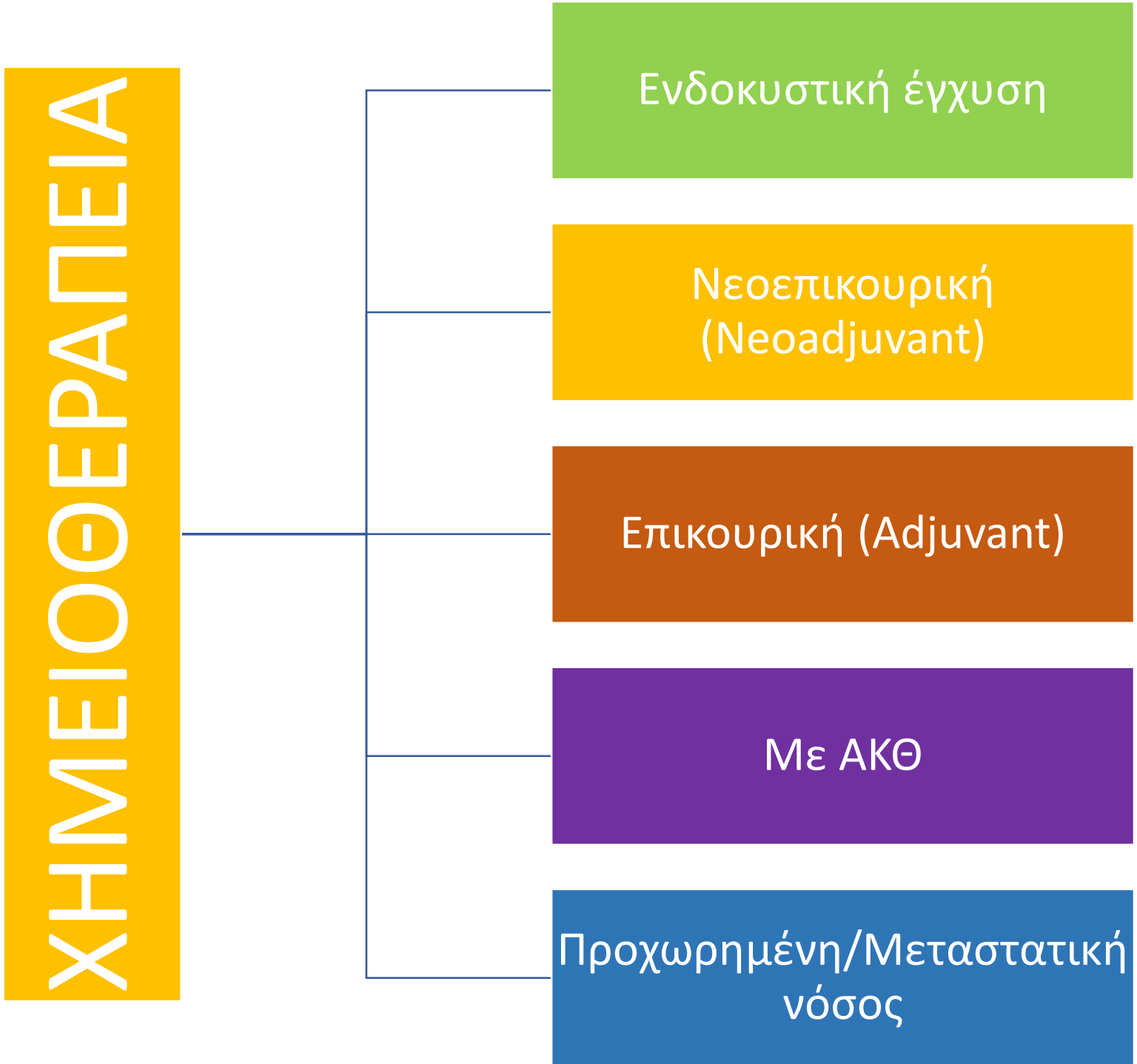
18-22 Φεβρουαρίου 2019
Ξενοδοχείο Athens Marriott

Μυοδιηθητικός καρκίνος ουροδόχου κύστης

<u>(Νεο)επικουρική χημειοθεραπεία και αντιμετώπιση μεταστατικής νόσου</u>

ΑΘΗΝΑ, 19 Φεβρουαρίου 2019

Ευθύμιος Κωστούρος
Παθολόγος Ογκολόγος, Επιμ. Β
Θεραπευτική κλινική ΕΚΠΑ
Γ.Ν.Α.«Αλεξάνδρα»


ΧΗΜΕΙΟΘΕΡΑΠΕΙΑ
Ενδοκυστική έγχυση
Νεοεπικουρική (Neoadjuvant)
Επικουρική (Adjuvant)
Με ΑΚΘ
Προχωρημένη/Μεταστατική νόσος

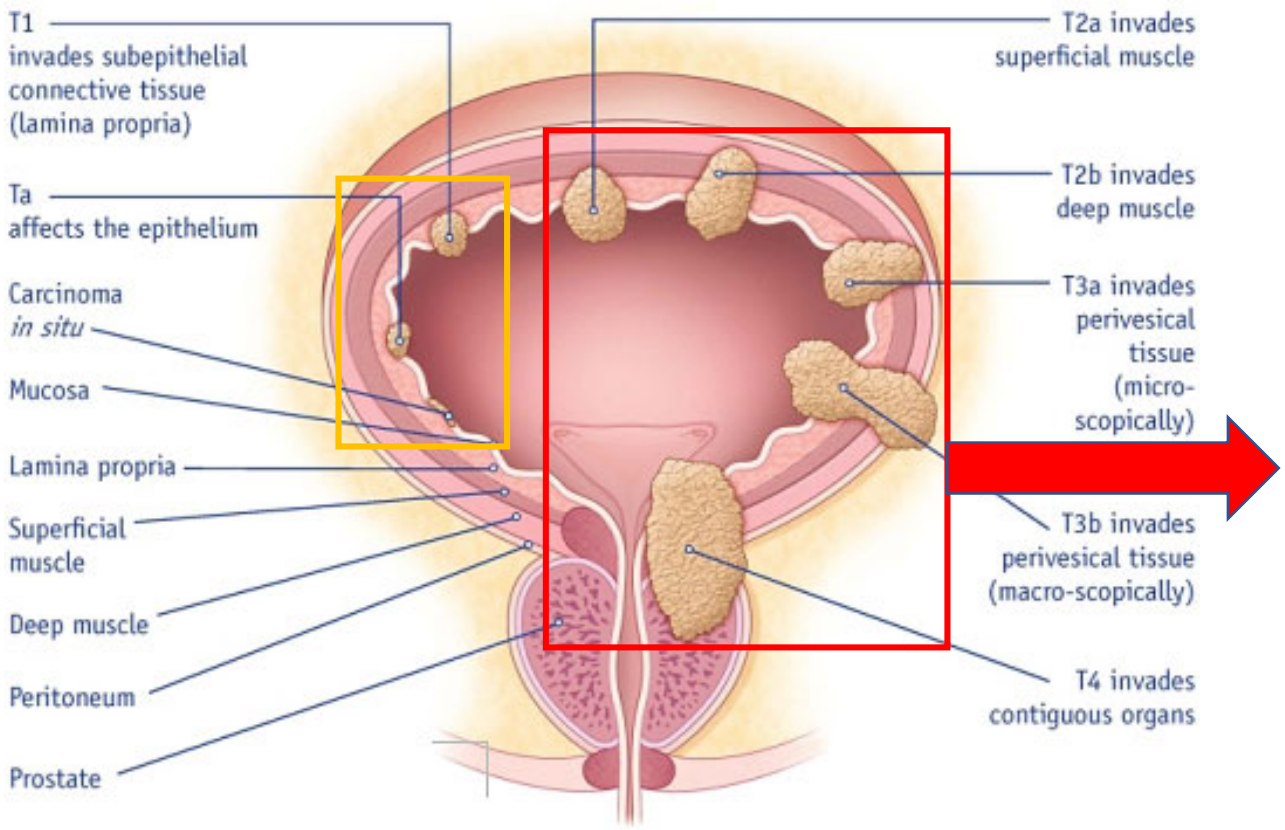
Επιδημιολογία

- 151.297 νέες περιπτώσεις/έτος , Ευρώπη
- 52.395 θάνατοι/έτος, Ευρώπη
- Άνδρες: 4ος πιο συχνός καρκίνος
- Γυναίκες: 7ος πιο συχνός καρκίνος
- Άνδρες/Γυναίκες : 5/1
- 70%: > 65 ετών
- Επίπτωση: 20/100.000/έτος
- Θνησιμότητα: 7/100.000/έτος

Καρκίνος ουροθηλίου

- 75%: μη διηθητικός - (pTis, pTa, pT1) ➡ 10-25% σε διηθητικό
- 25%: διηθητικός καρκίνος (Μυο-διηθητικός)(pT2, pT3, pT4)

- 5%: μεταστατική νόσος (N+,M+)



50%: μεταστάσεις

Primary Tumor (T)

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Ta	Noninvasive papillary carcinoma
Tis	Carcinoma in situ: "flat tumor"
T1	Tumor invades subepithelial connective tissue
T2	Tumor invades muscularis propria
pT2a	Tumor invades superficial muscularis propria (inner half)
pT2b	Tumor invades deep muscularis propria (outer half)
T3	Tumor invades perivesical tissue
pT3a	Microscopically
pT3b	Macroscopically (extravesical mass)
T4	Tumor invades any of the following: prostatic stroma, seminal vesicles, uterus, vagina, pelvic wall, abdominal wall
T4a	Tumor invades prostatic stroma, uterus, vagina
T4b	Tumor invades pelvic wall, abdominal wall

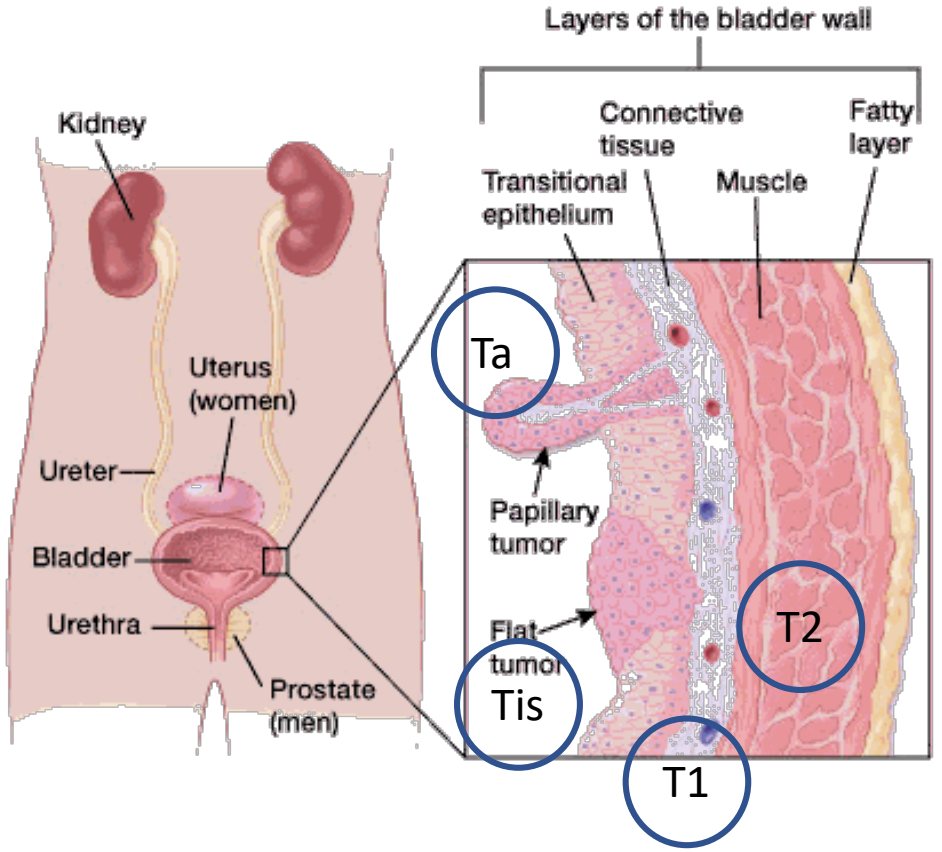
Regional Lymph Nodes (N)

Regional lymph nodes include both primary and secondary drainage regions. All other nodes above the aortic bifurcation are considered distant lymph nodes.

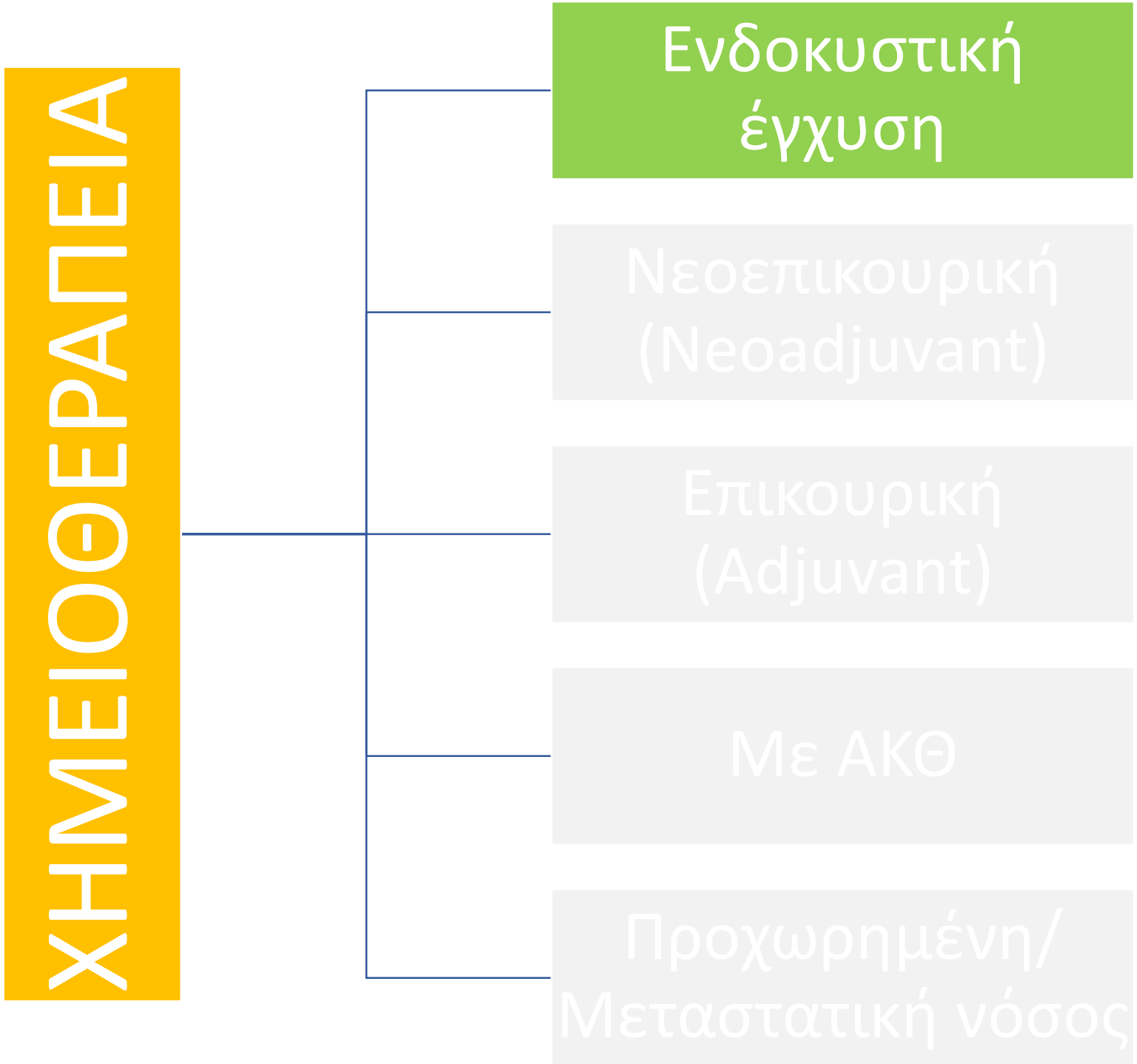
NX	Lymph nodes cannot be assessed
N0	No lymph node metastasis
N1	Single regional lymph node metastasis in the true pelvis (hypogastric, obturator, external iliac, or presacral lymph node)
N2	Multiple regional lymph node metastasis in the true pelvis (hypogastric, obturator, external iliac, or presacral lymph node metastasis)
N3	Lymph node metastasis to the common iliac lymph nodes

Distant Metastasis (M)

M0	No distant metastasis
M1	Distant metastasis



Stage I	T1	N0	M0
Stage II	T2a-T2b	N0	M0
Stage III	T3a-T3b, T4a	N0	M0
Stage IV	T4b	N0	M0
	Any T	N1-N3	M0
	Any T	Any N	M1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ΧΗΜΕΙΟΘΕΡΑΠΕΙΑ

- Ενδοκυστική έγχυση
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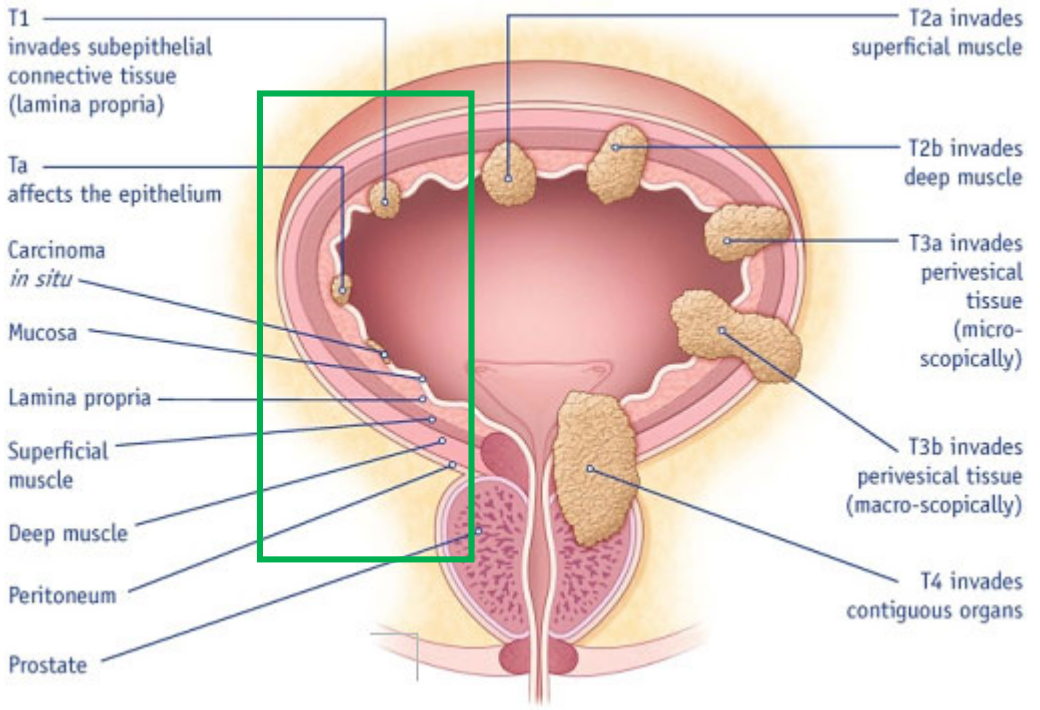
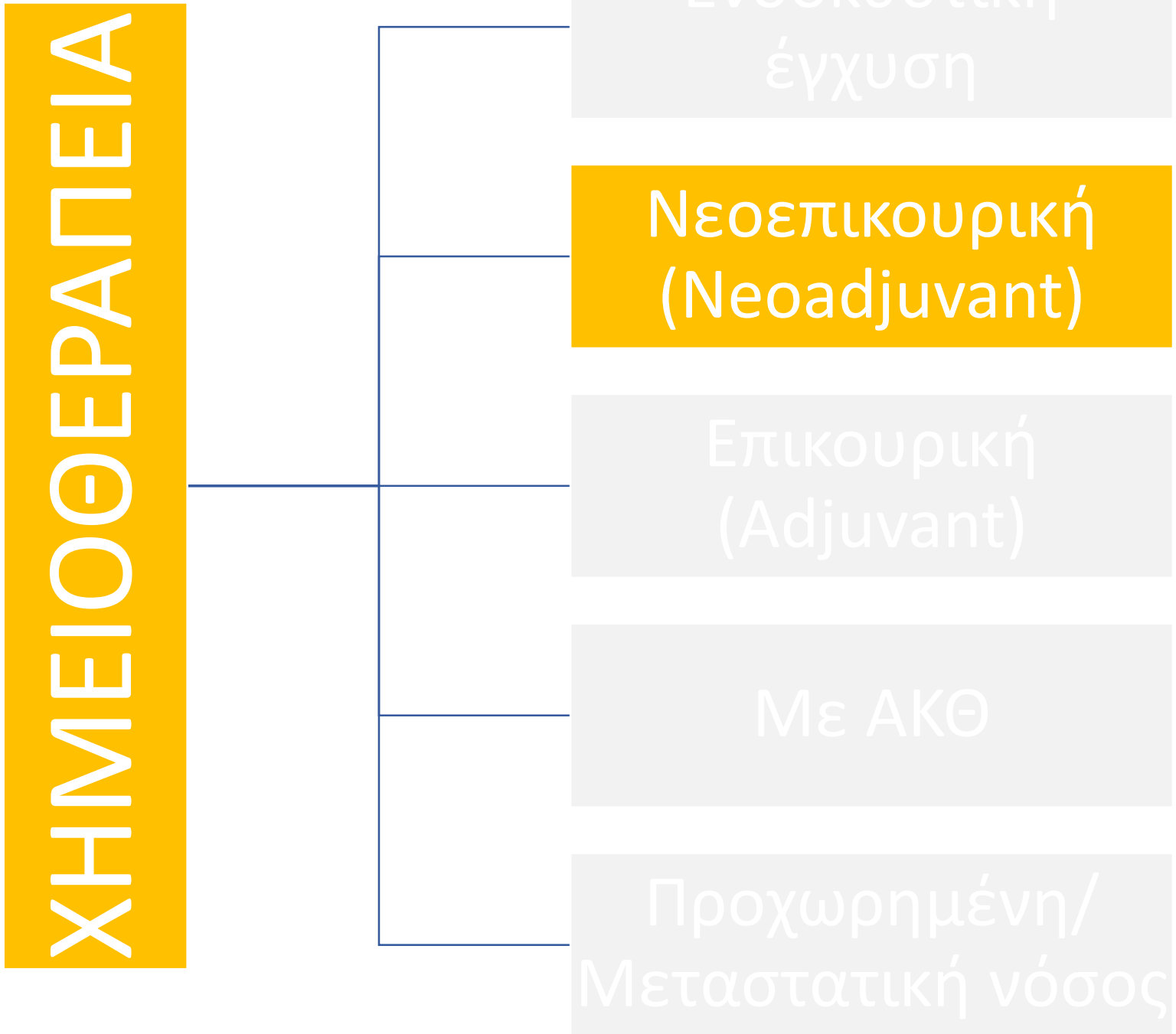


μετά από διουρηθρική εκτομή όγκου ουροδόχου κύστης για:
μη διηθητικό (Tis, Ta) καρκίνο
ελάχιστα διηθητικό (T1) καρκίνο

- low-grade Ta = χημειοθεραπεία (Μιτομυκίνη C, Επιρουβικίνη, Θειοτέπα, Δοξορουβικίνη, Γεμσιταμπίνη, Βαλρουμπισίνη)
- high-grade Ta και T1 tumors (low- and high-grade) = BCG (Bacillus Calmette Guerin)
  μία φορά την εβδομάδα x 6weeks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= Εισαγωγική

ΧΗΜΕΙΟΘΕΡΑΠΕΙΑ

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- **Νεοεπικουρική (Neoadjuvant)**
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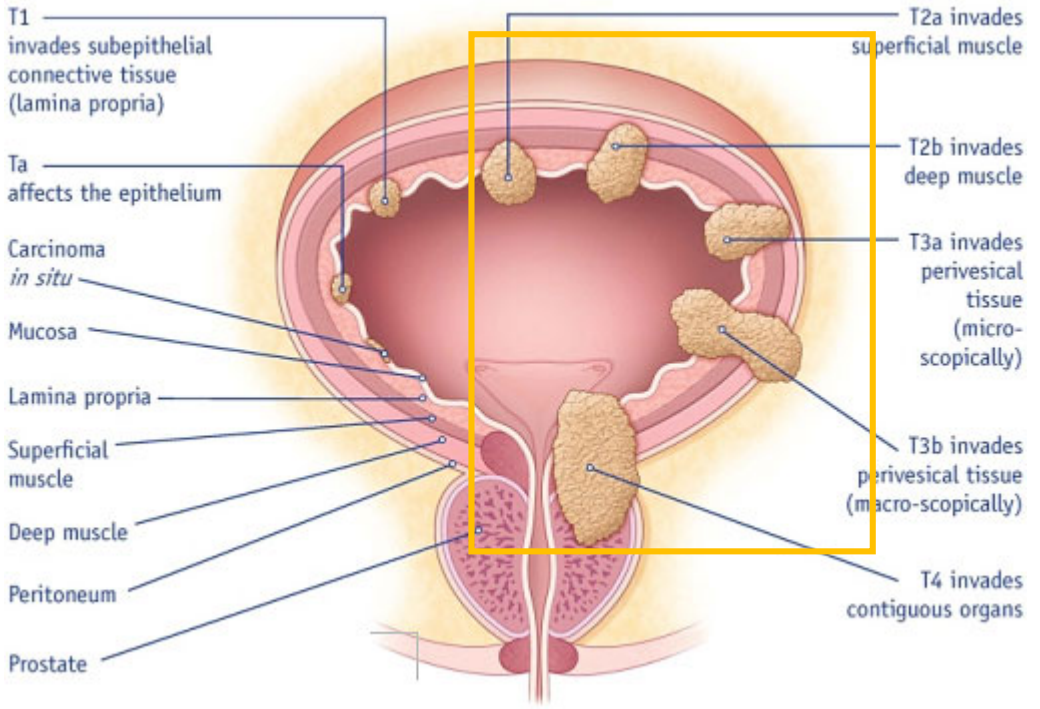

>T2, Μυοδιηθητική νόσος
(High grade νόσος)

ΓΙΑΤΙ;

Όφελος στην **συνολική επιβίωση (OS)** με:

θεραπεία μικρομεταστατικής νόσου
υποσταδιοποίηση

ΧΗΜΕΙΟΘΕΡΑΠΕΙΑ

- Ενδοκυστική έγχυση
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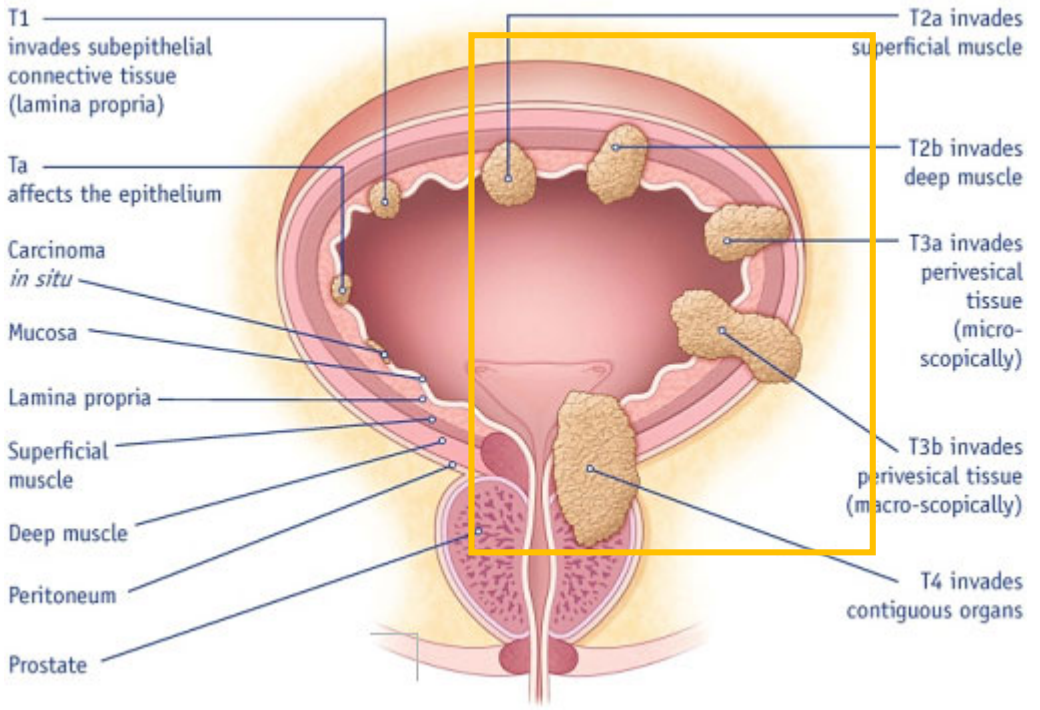
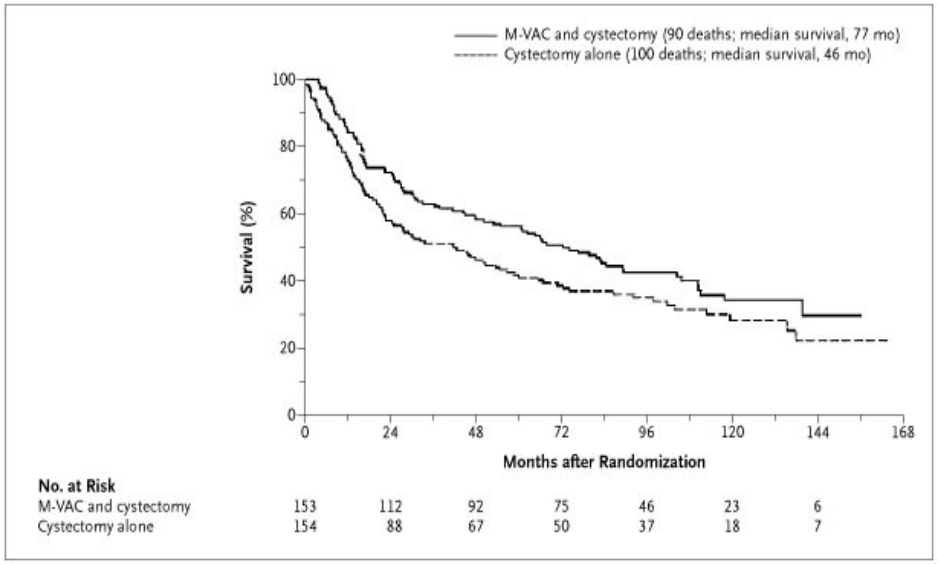
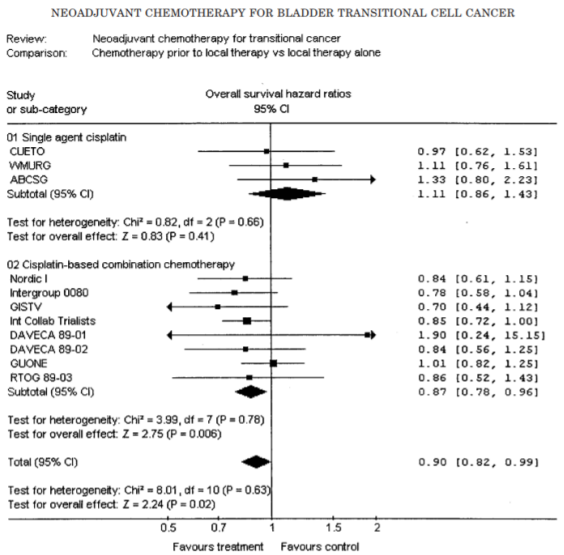


>T2, Μυοδιηθητική νόσος
(High grade νόσος)

Grossman, H. B. et al. N Engl J Med 2003;349:859-866

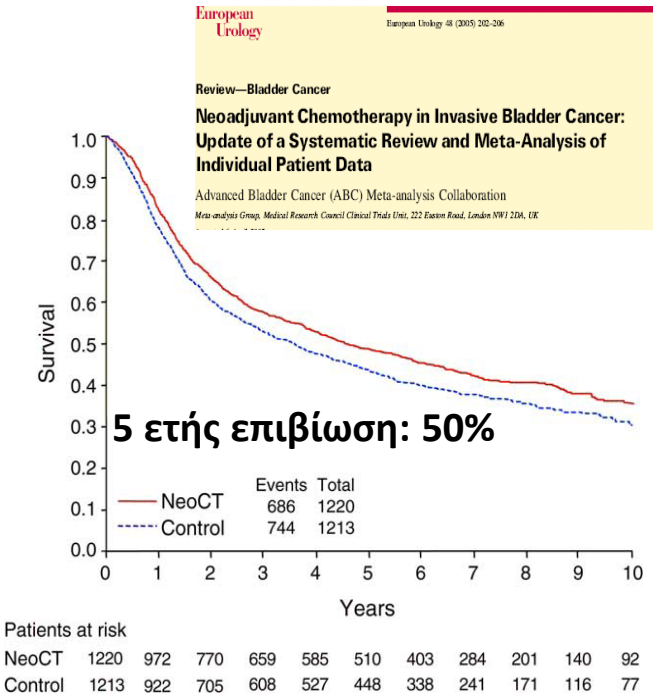


Winquist E et al. J Urol 2004;171:561-569



Απόλυτο όφελος επιβίωσης: 6.5%
από 50% σε 56.5%

Eur Urol 2005



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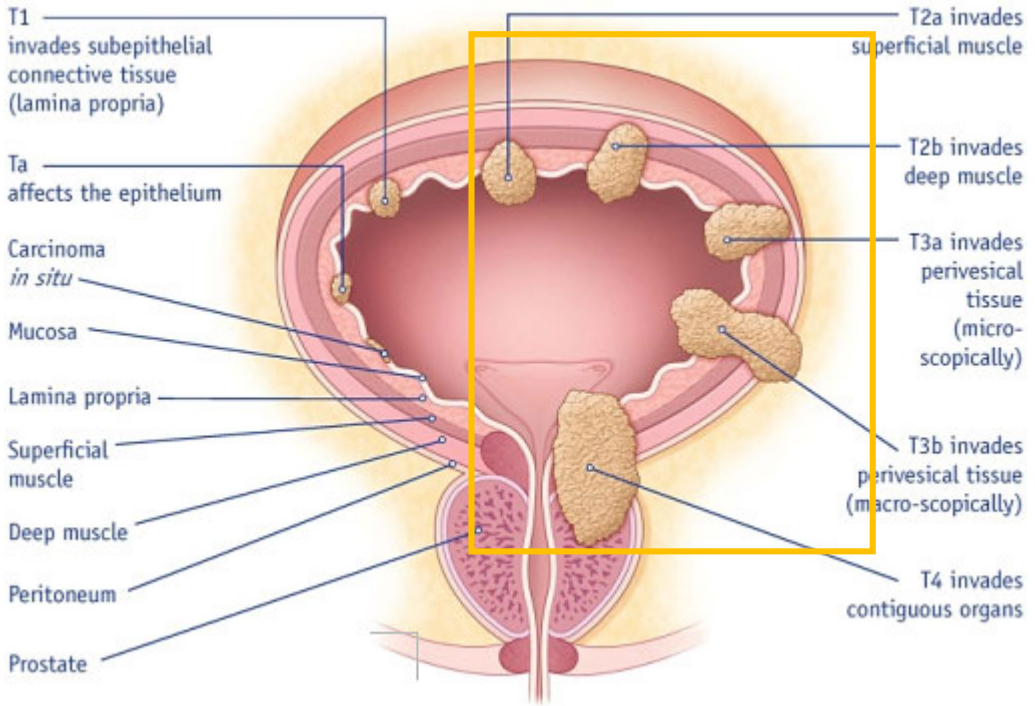


>T2, Μυοδιηθητική νόσος
(High grade νόσος)

- Ουροθηλιακός καρκίνος ανώτερου ουροποιητικού (Higher stage & Higher grade), λόγω μείωσης νεφρικής λειτουργίας μετά από νεφροουρητηρεκτομή
- Υδρονέφρωση
- LNs +

Apolo AB et al, Am Soc Clin Oncol Educ Book, 2015.35:105-112

	Stadler (p53)	Cognetti	Paz-Ares	Sternberg	Grossman	MRC/EORTC
Chemotherapy	Adjuvant MVAC × 3	Adjuvant GC × 4	Adjuvant PGC × 4	Adjuvant ddMVAC/ GC/MVAC × 4	Neoadjuvant MVAC	Neoadjuvant CMV
Patients	T1 and T2 negative LN	T2G3, T3 to T4, N0-2	T3 to T4, N0 to N2	T3 to T4 and/or pT × N1 to N3	T2 to T4aN0	T2 to T4aN0
Design						
α error	5%	5%	5%	5%	5%	5%
Power	90%	80%	80%	80%	80%	90%
Endpoint	Recurrence	OS	OS	OS	OS	OS
	0.5 to 0.3 at 3 years (20%)	50% to > 60% at 2 years (10%)	50% to > 65% at 2 years (15%)	35% to > 42% at 5 years (7%)	35% to > 42% median OS (50%)	50% to > 60% at 2 years (10%)
Hazard Ratio	0.52	0.75	0.77	0.826		
Planned Sample Size	190	610	340	660 (originally 1,344)	298	915
Results						
Patients randomized	114 (499 tested and 272 +p53)	192	142	284	307	976
Years to Accrue	9	6	7	6	11	6
5-Year Recurrence (Observation vs Chemotherapy)	TTR, 0.20; p = 0.62; HR, 0.78	DFS, 42.3% vs. 37.2%; p = 0.70; HR, 1.08; all, 40%	3 years 44% vs. 73%; p < 0.0001; HR, 0.36; all, 54%	PFS, 31.8% vs. 47.6%; p = < 0.0001; HR, 0.54		5-year DFS, 32% vs. 39%; 10-year DFS, 20% vs. 27% p = 0.008; HR, 0.82
5-Year OS (Observation vs. Chemotherapy)	85% (both arms)	53.7% vs. 43.4%; p = 0.24; HR, 1.29; all, 48.5%	31% vs. 60%; p < 0.0009; HR, 0.44; all, 49%	47.7% vs. 53.6%; p = 0.13; HR, 0.78; all, 38.6%	43% vs. 57%; p = 0.06	5-year OS, 43% vs. 49%; 10-year OS, 30% vs. 36%; p = 0.037; HR, 0.84
Median Follow-up	5.4 years	35 months	30 months	7 years	8.7 years	8 years

Abbreviations: CMV, cisplatin/methotrexate/vinblastine; dd, dose-dense; DFS, disease-free survival; EORTC, European Organisation for Research and Treatment of Cancer; GC, gemcitabine/cisplatin; HR, hazard ratio; MVAC, methotrexate/vinblastine/doxorubicin/cisplatin; OS, overall survival; PFS, progression-free survival; PGC, paclitaxel/gemcitabine/cisplatin; TTR, time to progression.

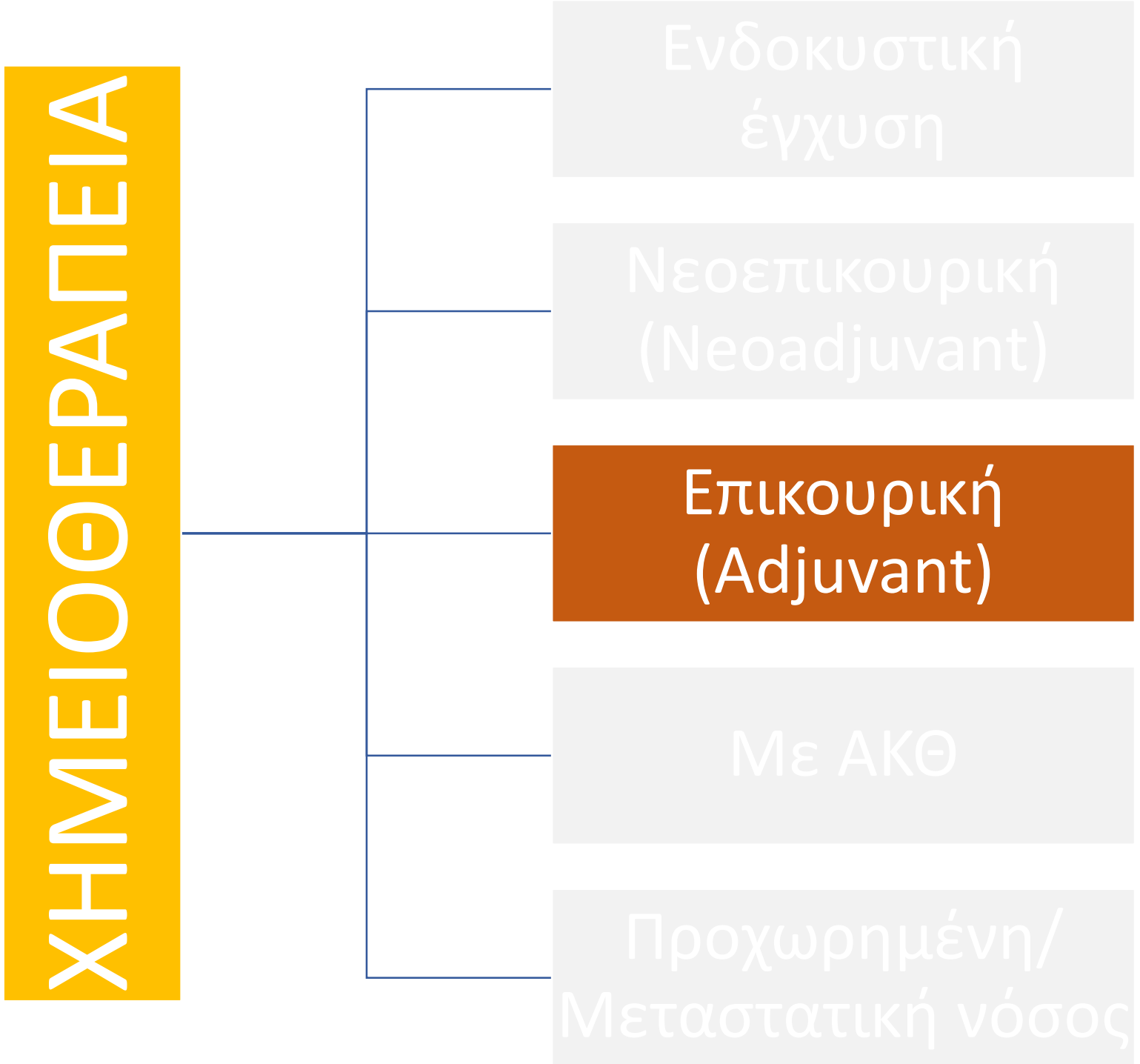
Σχήματα Χημειοθεραπείας

Cisplatin-based neoadjuvant chemotherapy (dd-MVAC, GC) x 3-4 cycles

GC εναλλακτικό του dd-MVAC, λόγω ισοδυναμίας στην προχωρημένη νόσο, δεν υπάρχει αντίστοιχη ένδειξη στη νεοεπικουρική και επικουρική θεραπεία

ddMVAC: dose-dense MVAC, / GC: Gemcitabine, Cisplatin

όχι carboplatin, αν δεν χορηγηθεί cisplatin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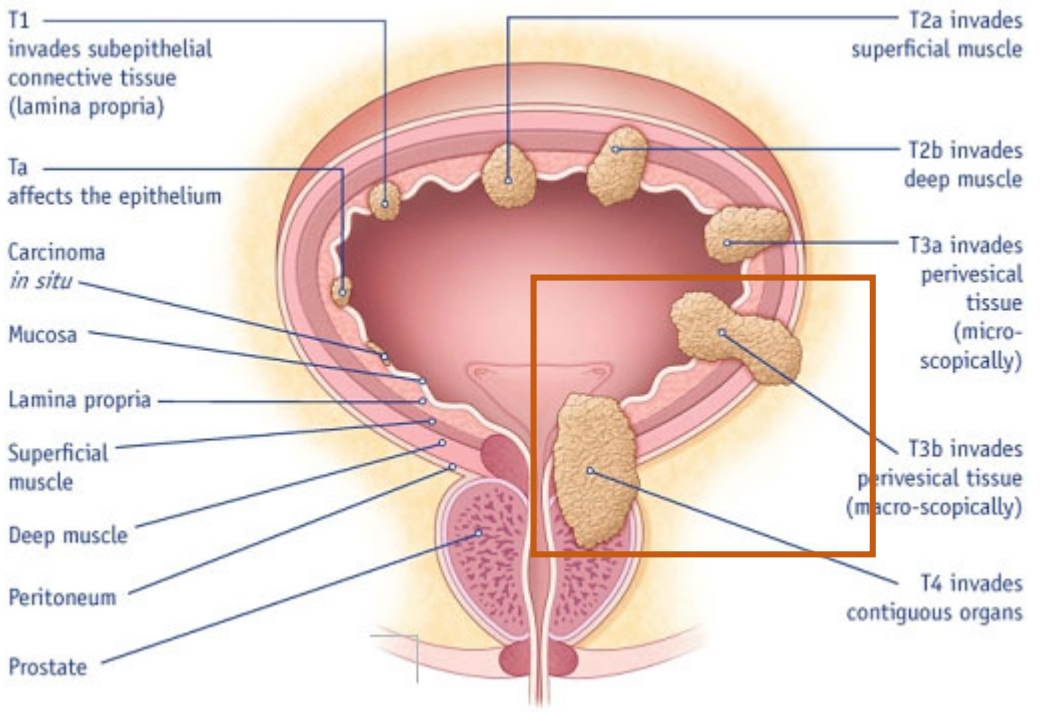

- T3-T4, N+ νόσος (High risk patients),

Αν δεν έχει γίνει νεοεπικουρική

ΓΙΑΤΙ;

Όφελος στην **συνολική επιβίωση (OS)** και στην **επιβίωση ελευθέρας νόσου (DFS)**:

θεραπεία μικρομεταστατικής νόσου

- ✓ Καλύτερη φυσική κατάσταση ασθενούς στην κυστεκτομή
- Μετεγχειρητική νοσηρότητα (καθυστέρηση ΧΜΘ)

ΧΗΜΕΙΟΘΕΡΑΠΕΙΑ

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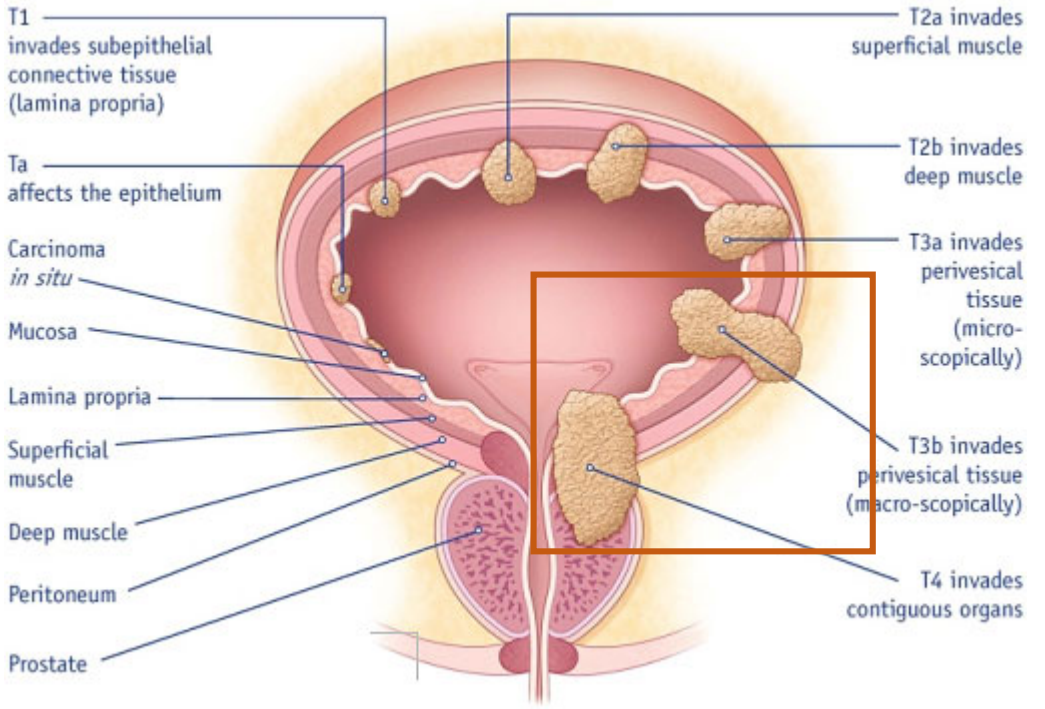
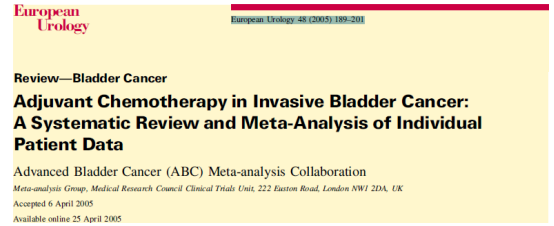


- T3-T4, N+ νόσος (High risk patients)

Μετα-ανάλυση (1990-1996) (6 μελέτες)

European Urology 48 (2005) 189–201


European Urology 48 (2005) 189–201

Review—Bladder Cancer

Adjuvant Chemotherapy in Invasive Bladder Cancer: A Systematic Review and Meta-Analysis of Individual Patient Data

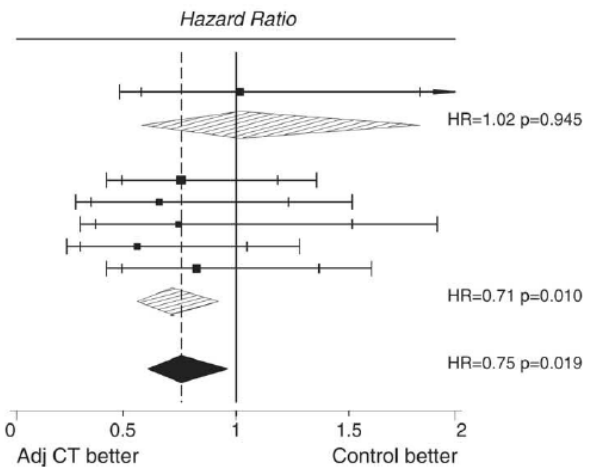
Advanced Bladder Cancer (ABC) Meta-analysis Collaboration

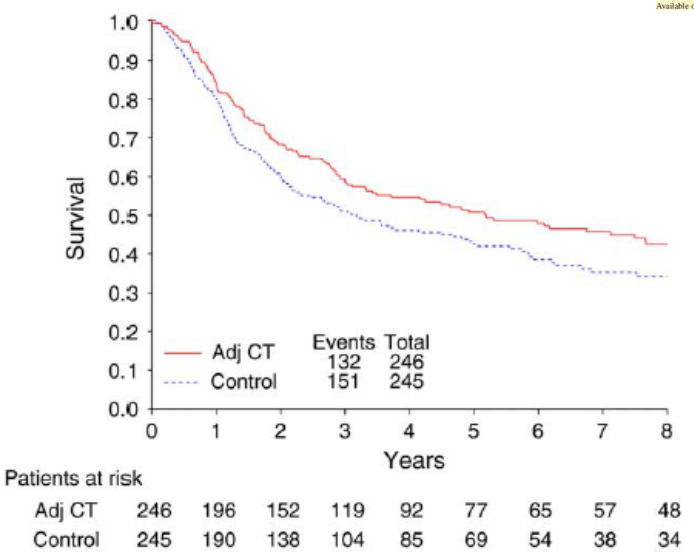
Meta-analysis Group, Medical Research Council Clinical Trials Unit, 222 Euston Road, London NW1 2DA, UK

Accepted 6 April 2005

Available online 25 April 2005

	(no. events/no. entered) Adj CT	Control	O-E	Variance
Single agent cisplatin				
Studer	23/46	22/45	0.23	11.03
Sub-total	23/46	22/45	0.23	11.03
Cisplatin-based combinations				
Skinner	34/50	40/52	-5.24	18.39
Bono	14/43	23/47	-3.91	9.04
Freiha	13/26	17/25	-2.18	7.39
Stockle	20/26	20/23	-5.48	9.07
Otto	28/55	29/53	-2.86	14.11
Sub-total	109/200	129/200	-19.66	58.00
Total	132/246	151/245	-19.43	69.03





Adjuvant CT:

5-ετής επιβίωση: 51%

Απόλυτη βελτίωση επιβίωσης **9%** (95% CI 1% -16%) **στα 3 χρόνια**

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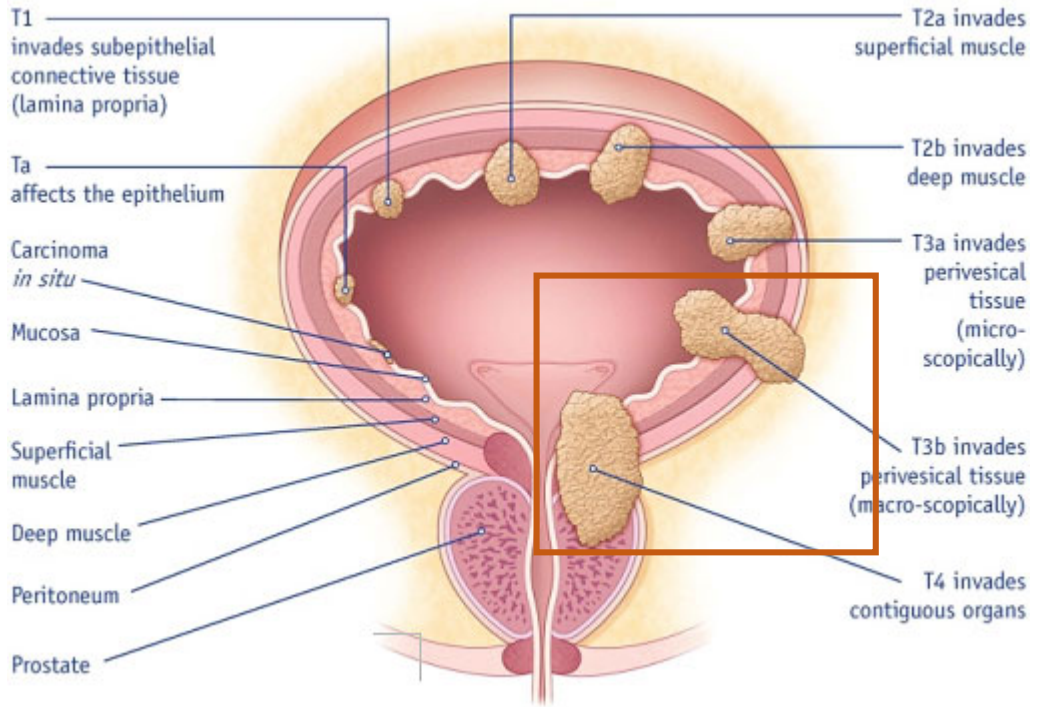

- T3-T4, N+ νόσος (High risk patients)

1η αναφορά στο MVAC

J Urol.**1985** Mar;133(3):403-7.

Format: Abstract Send to

J Urol. 1985 Mar;133(3):403-7.

Preliminary results of M-VAC (methotrexate, vinblastine, doxorubicin and cisplatin) for transitional cell carcinoma of the urothelium.

Sternberg CN, Yagoda A, Scher HI, Watson RC, Ahmed T, Weiselberg LR, Geller N, Hollander PS, Herr HW, Sogani PC, et al.

Abstract

The M-VAC (methotrexate, vinblastine, doxorubicin and cisplatin) regimen was used to treat 25 patients with transitional cell carcinoma of the urothelial tract. Treatment consisted of monthly cycles of 30 mg. per m.2 methotrexate, followed 24 hours later by 3 mg. per m.2 vinblastine, 30 mg. per m.2 doxorubicin and 70 mg. per m.2 cisplatin, and concluded with repeat vinblastine and methotrexate on days 15 and 22. Significant tumor regression was noted in 71 per cent of the patients. Complete clinical remission was observed in 12 of 24 patients (50 per cent, 95 per cent confidence limits 30 to 70 per cent) with bidimensionally measurable indicator lesions, 6 of whom had pathological confirmation. After surgical exploration 4 patients required downstaging to a partial remission. The median duration of response has not yet been reached at 9.5 plus months, range 4.5 plus to 16 plus. Five patients (21 per cent) had a partial clinical remission for 4 to 8 plus months, 1 had a minor response for 4 months and 1 had stable disease for 11 months. All metastatic sites responded, including bone (6 of 8 cases), liver (3 of 5), locoregional (12 of 17) and intravesical (6 of 7) disease. Toxicity included moderately severe myelosuppression that resulted in nadir sepsis in 4 patients and a drug-related death in 1, mild to moderate anorexia, vomiting, alopecia and renal dysfunction. These preliminary results suggest that treatment with methotrexate, vinblastine, doxorubicin and cisplatin is extremely effective against locoregional and disseminated urothelial tract tumors, with the expectation (95 per cent confidence limits) of inducing objective tumor regression in 53 to 89 per cent of the cases.

PMID: 4000740

Σχήματα Χημειοθεραπείας

Cisplatin-based adjuvant chemotherapy (dd-MVAC, GC, CMV) x 3-4 cycles

GC εναλλακτικό του dd-MVAC, λόγω ισοδυναμίας στην προχωρημένη νόσο, δεν υπάρχει αντίστοιχη ένδειξη στην επικουρική και επικουρική θεραπεία

ddMVAC: dose-dense MVAC, / GC: Gemcitabine, Cisplatin/
CMV: Cisplatin, Methotrexate, Vinblastine

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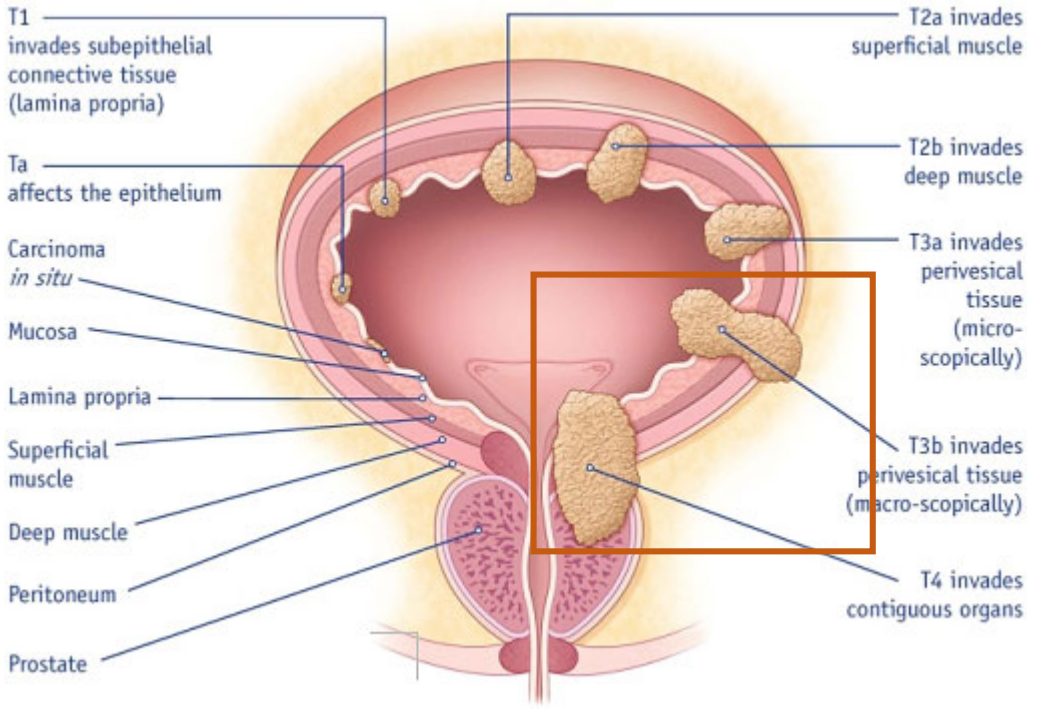
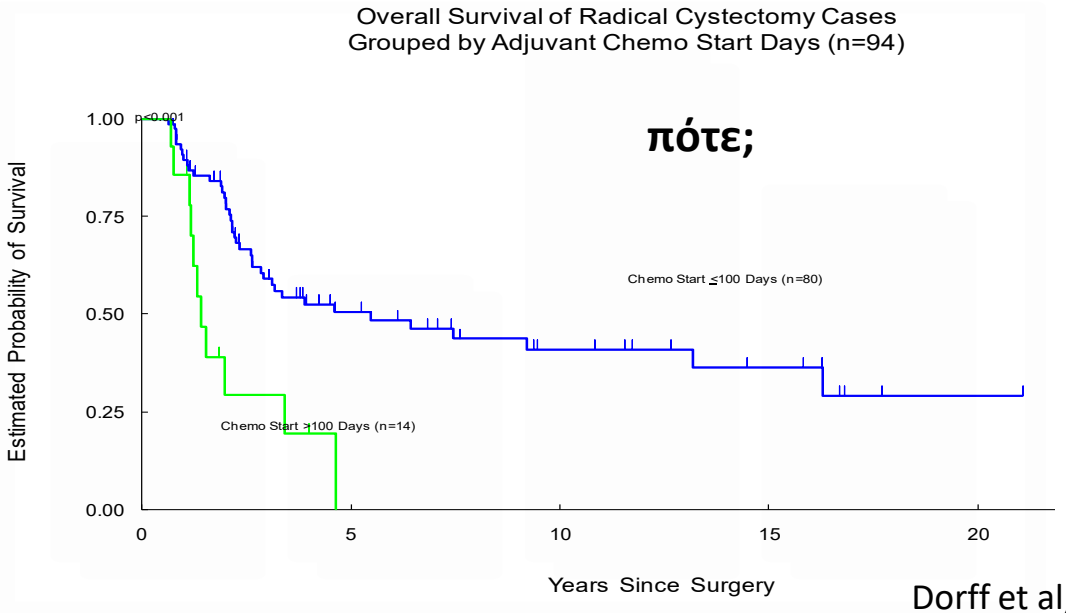
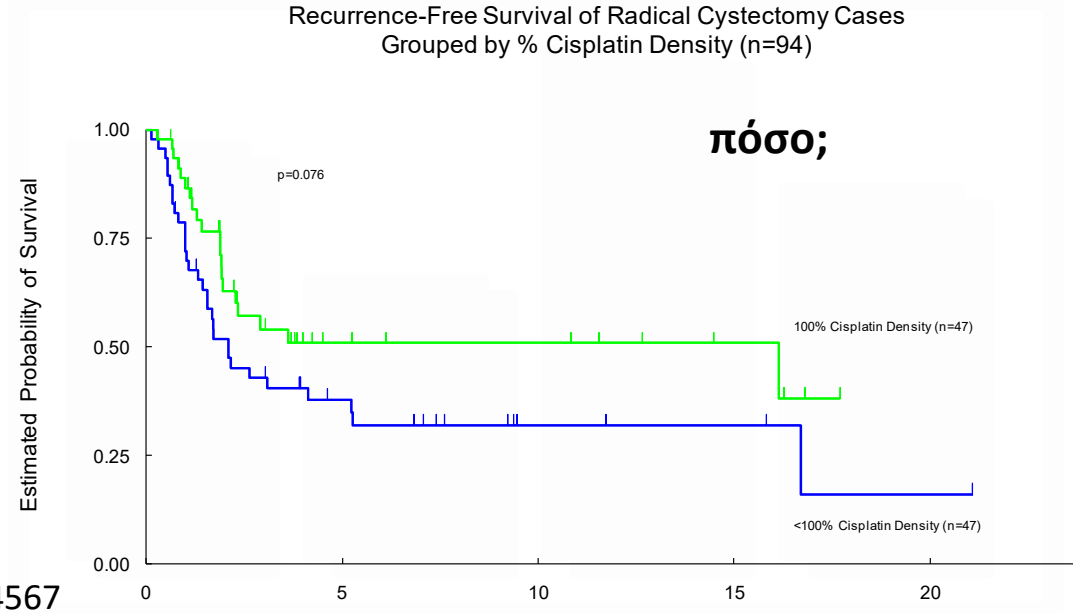
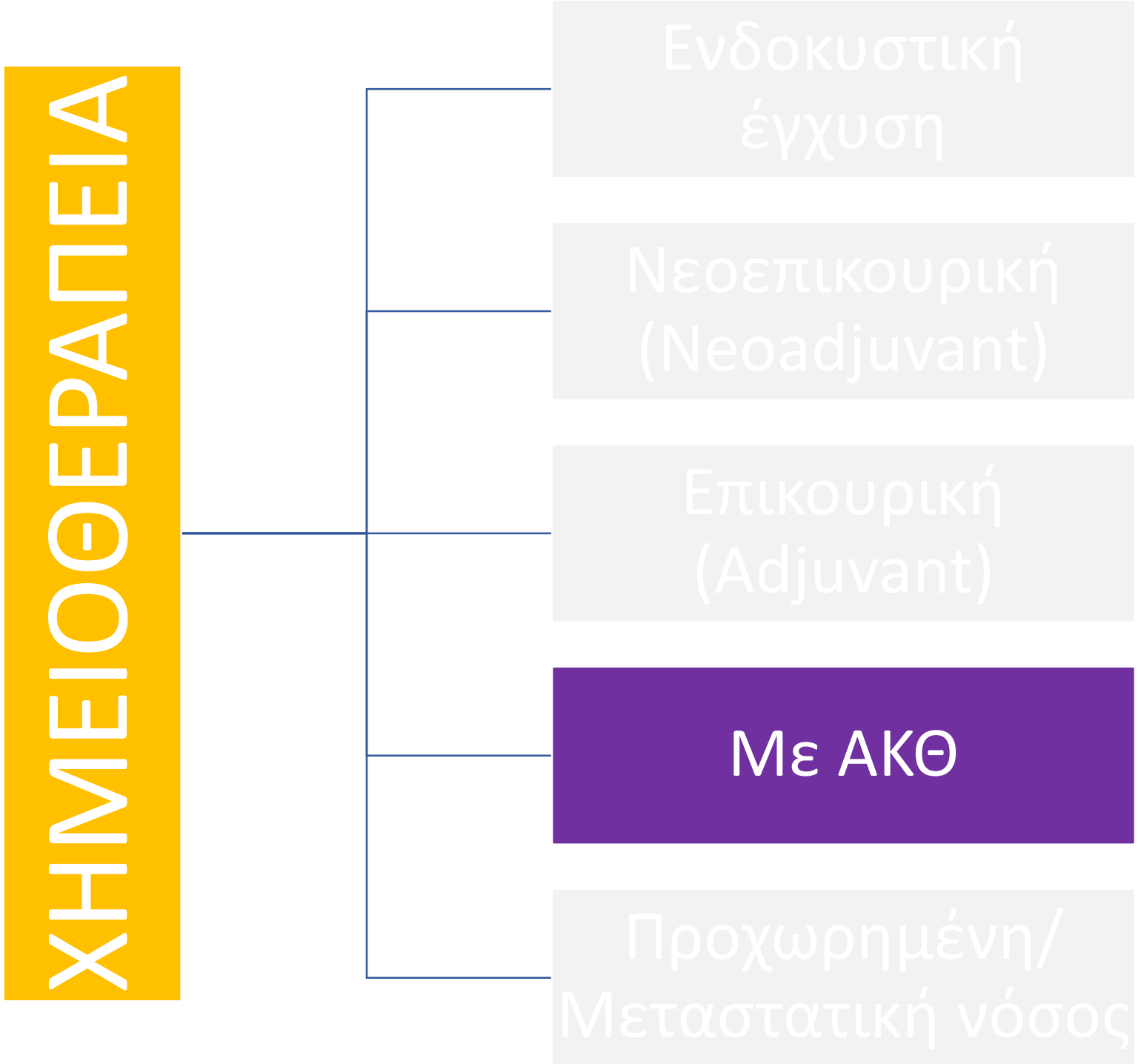


- T3-T4, N+ νόσος (High risk patients)



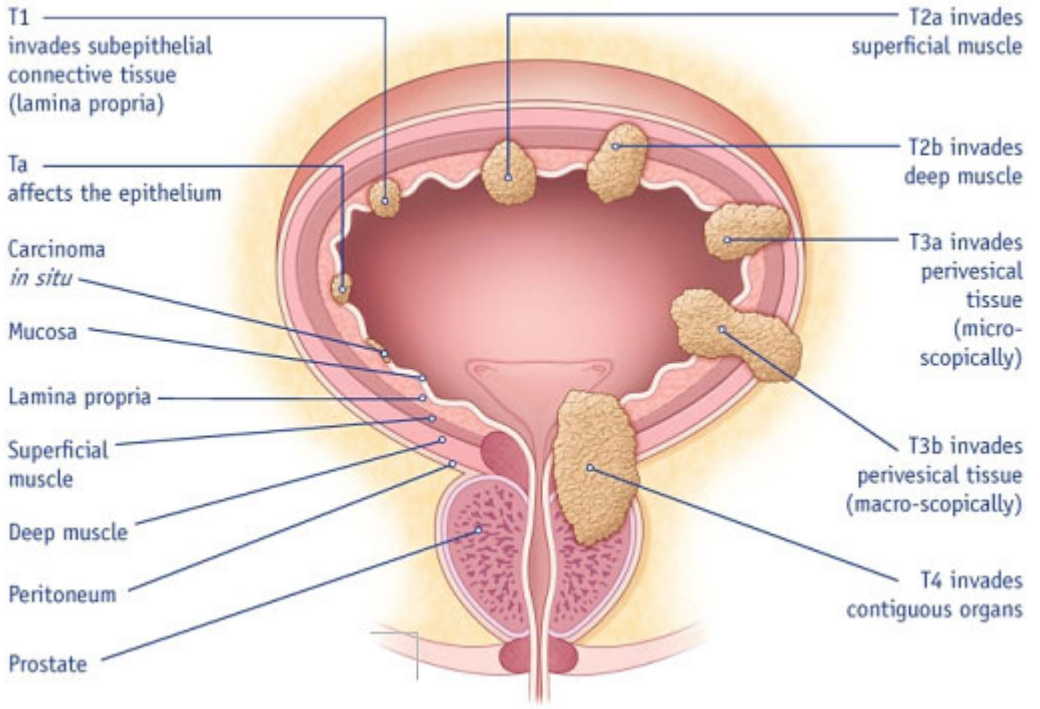


Dorff et al, ASCO 2010, abstr 4567


ΧΗΜΕΙΟΘΕΡΑΠΕΙΑ
Ενδοκυστική έγχυση
Νεοεπικουρική (Neoadjuvant)
Επικουρική (Adjuvant)
Με ΑΚΘ
Προχωρημένη/ Μεταστατική νόσος

ΧΗΜΕΙΟΘΕΡΑΠΕΙΑ

- Ενδοκυστική έγχυση
- Νεοεπικουρική (Neoadjuvant)
- Επικουρική (Adjuvant)
- **Με ΑΚΘ**
- Προχωρημένη/ Μεταστατική νόσος



Πότε;

- ❑ Θεραπεία διατήρησης ουροδόχου κύστης:
  α) άρνηση κυστεκτομής
  β) unfit για χειρουργείο (λόγω συννοσηρότητας)

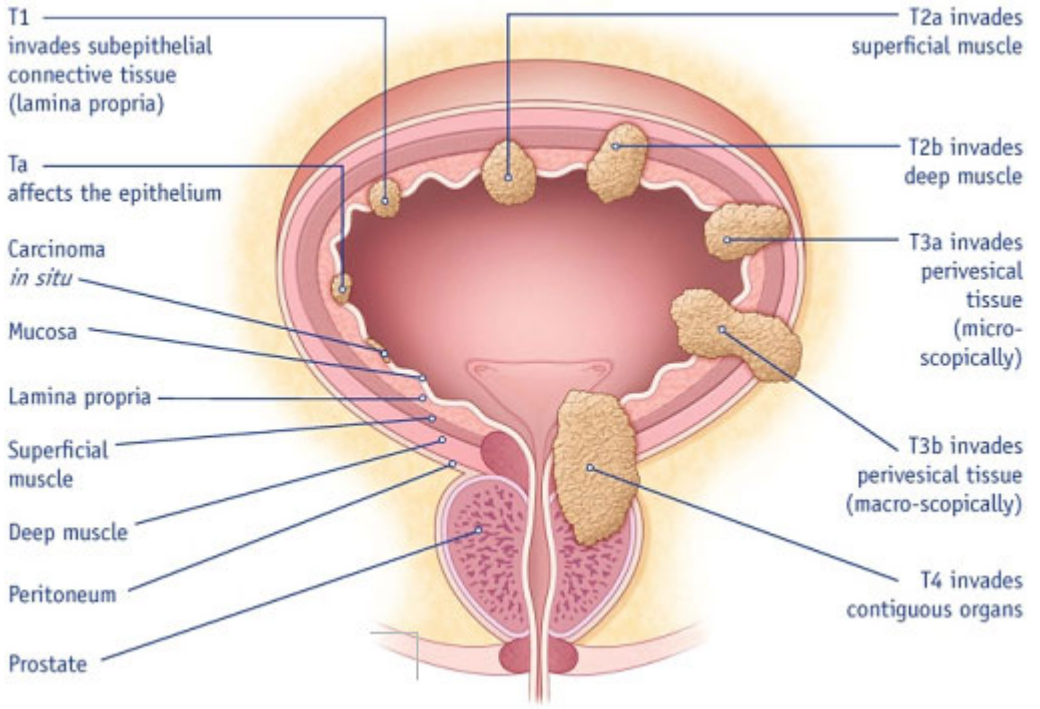
Προϋποθέσεις:

- όγκοι Τ2, Τ3α
- όχι υδρονέφρωση
- όχι εκτεταμένο CIS
- Καλή νεφρική λειτουργία

- ❑ Προχωρημένη νόσος (παρηγορητική θεραπεία):
  a) Μεταστάσεις
  b) Πυελική υποτροπή

ΧΗΜΕΙΟΘΕΡΑΠΕΙΑ

- Ενδοκυστική έγχυση
- Νεοεπικουρική (Neoadjuvant)
- Επικουρική (Adjuvant)
- **Με ΑΚΘ**
- Προχωρημένη/ Μεταστατική νόσος



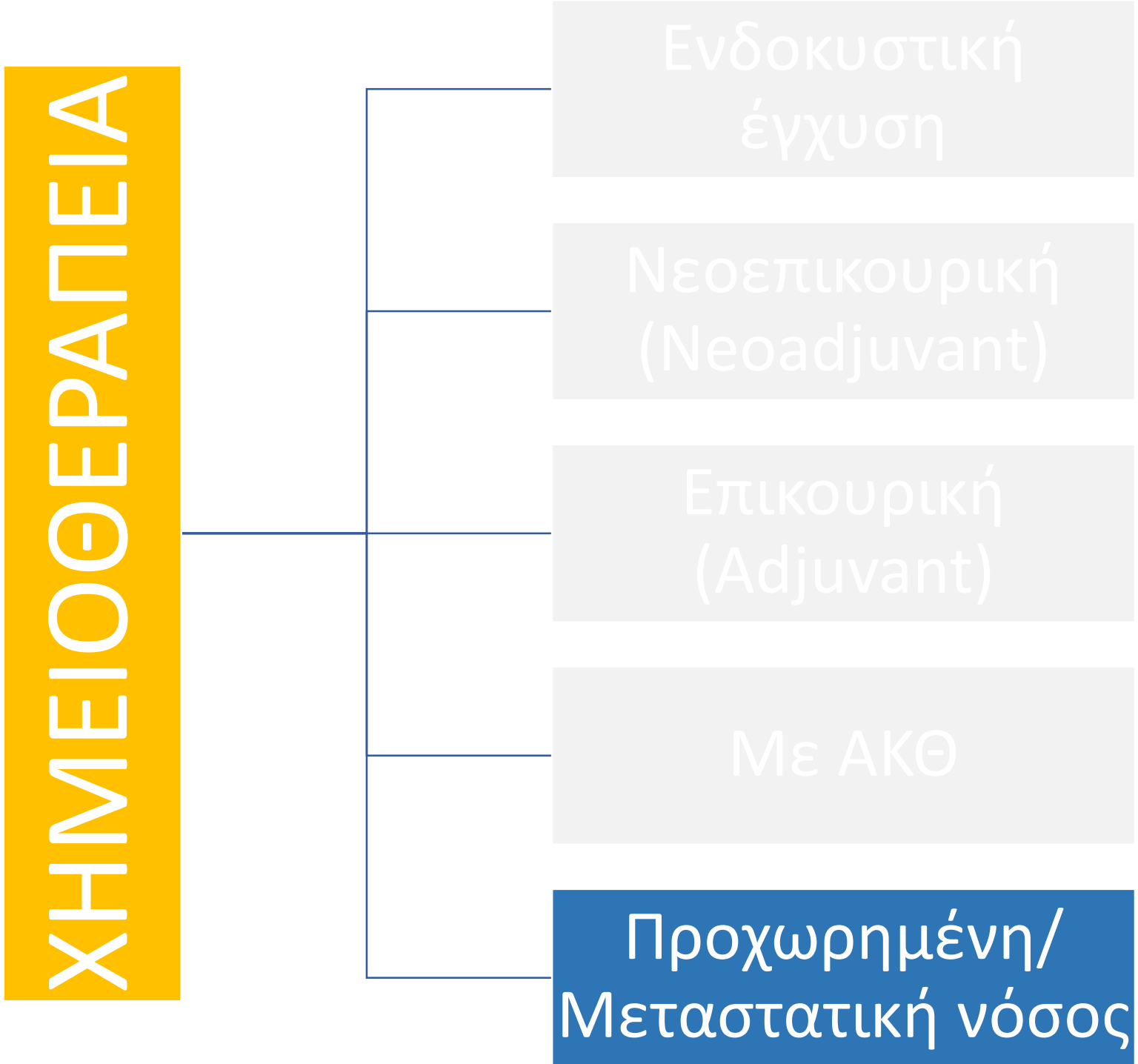
Σχήματα Χημειοθεραπείας

- Θεραπεία διατήρησης ουροδόχου κύστης:
  Cisplatin,
  Cisplatin & 5FU,
  5FU & Mytomycin-C,
  Cisplatin & Paclitaxel

Σχήματα Χημειοθεραπείας

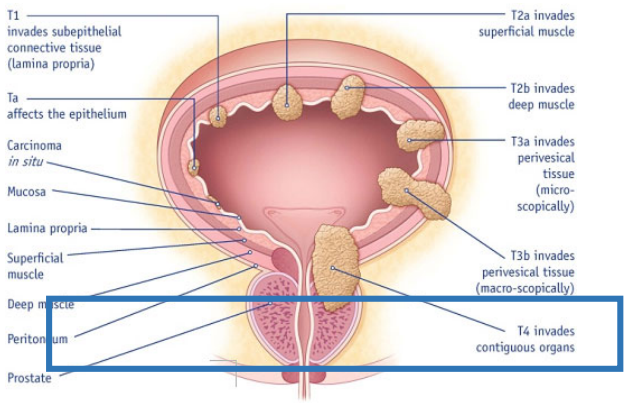
- Προχωρημένη νόσος (παρηγορητική θεραπεία) :
  Cisplatin,
  Docetaxel/Paclitaxel,
  5FU,
  5FU & Mytomycin-C,

  Capecitabine,
  χαμηλής δόσης Gemcitabine


ΧΗΜΕΙΟΘΕΡΑΠΕΙΑ
Ενδοκυστική έγχυση
Νεοεπικουρική (Neoadjuvant)
Επικουρική (Adjuvant)
Με ΑΚΘ
Προχωρημένη/ Μεταστατική νόσος

ΧΗΜΕΙΟΘΕΡΑΠΕΙΑ

- Ενδοκυστική έγχυση
- Νεοεπικουρική (Neoadjuvant)
- Επικουρική (Adjuvant)
- Με ΑΚΘ
- **Προχωρημένη/ Μεταστατική νόσος**



c**T4b**N0M0
cTany**N1-3**M0
cTanyNany**M1**

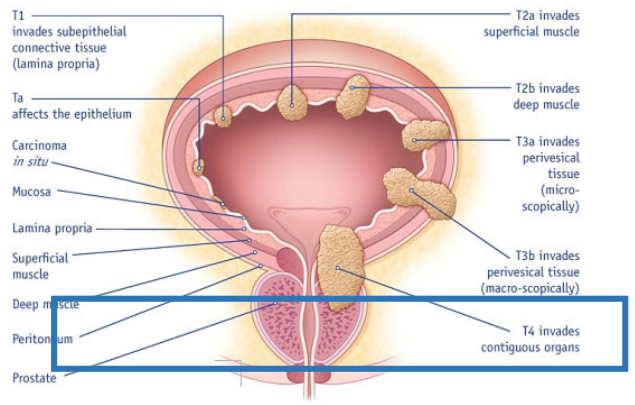
Που;
LNs, Lung, Liver
Bone, CNS

Πρόγνωση

- Median survival in these patients is about 14 months
- 5-ετής επιβίωση: <15%

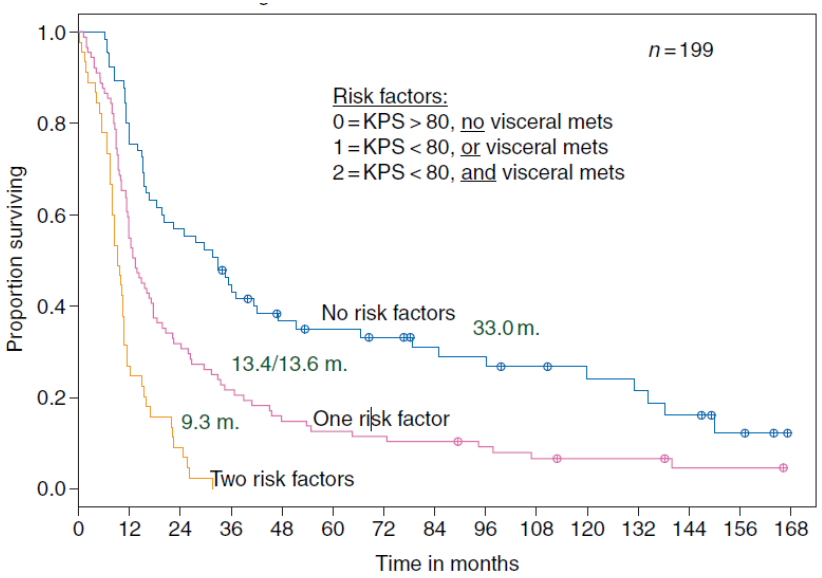
ΧΗΜΕΙΟΘΕΡΑΠΕΙΑ

- Ενδοκυστική έγχυση
- Νεοεπικουρική (Neoadjuvant)
- Επικουρική (Adjuvant)
- Με ΑΚΘ
- Προχωρημένη/ Μεταστατική νόσος



c**T4b**N0M0
cTany**N1-3**M0
cTanyNany**M1**

Προγνωστικοί Παράγοντες
1ης γραμμής (KPS & Σπλαγχνικές μεταστάσεις)



Bajorin, D.F. et al. J Clin Oncol 1999; 17: 3173–3181

Προγνωστικοί Παράγοντες
2ης γραμμής (Hgb & Ηπατικές μεταστάσεις & ECOG-PS)

- 4 subgroups formed, based on the presence of 0, 1, 2 or 3 prognostic factors

Variables at baseline	Ref. category
Haemoglobin	< 10 g/dL
Liver involvement	No involvement
ECOG-PS	≥ 1

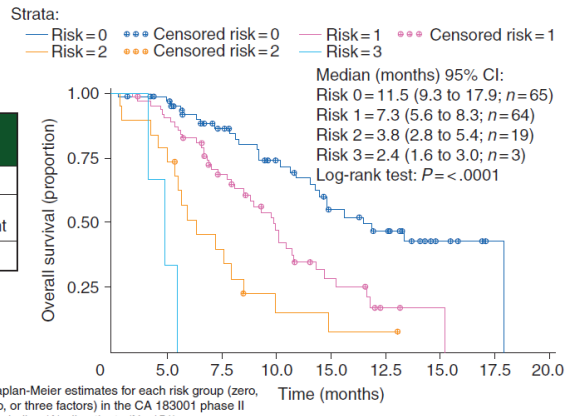


Fig2. Kaplan-Meier estimates for each risk group (zero, one, two, or three factors) in the CA 183001 phase II study, including (A) all patients (N = 151)

Kaplan-Meier estimates of each risk group

Bellmunt J, et al. J Clin Oncol. 2010;28:1850–1855

ΧΗΜΕΙΟΘΕΡΑΠΕΙΑ

- Ενδοκυστική έγχυση
- Νεοεπικουρική (Neoadjuvant)
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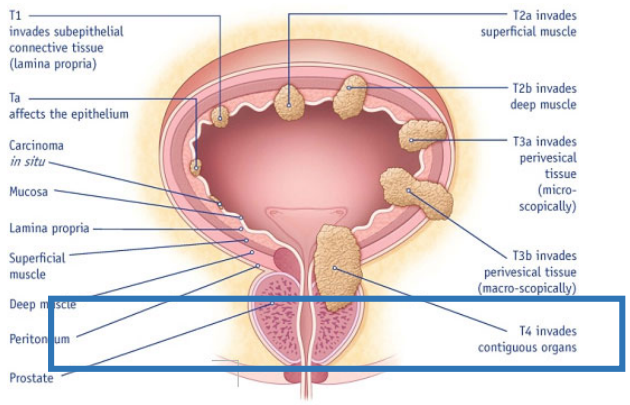
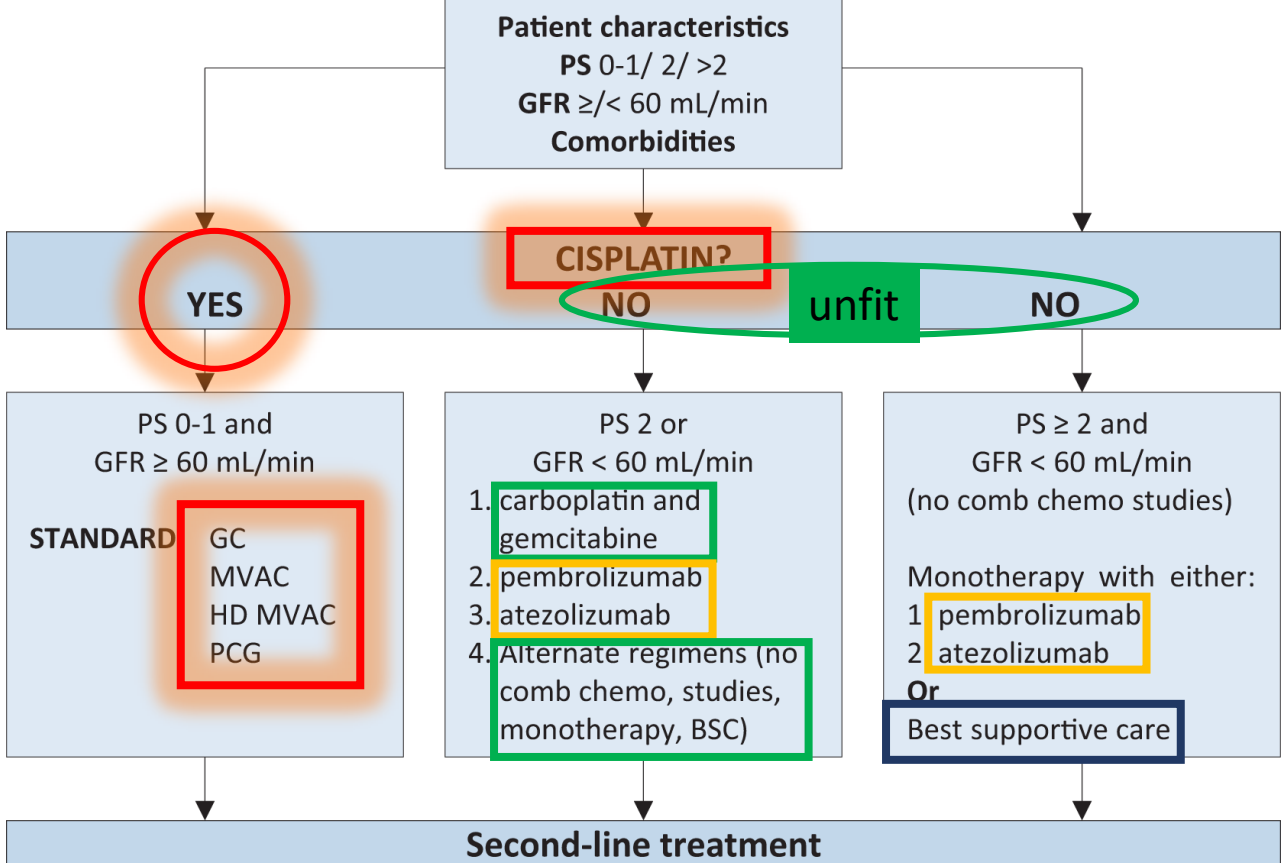
- Με ΑΚΘ
- Προχωρημένη/ Μεταστατική νόσος



c**T4b**N0M0
cTany**N1-3**M0
cTanyNany**M1**

EAU Guidelines 2019

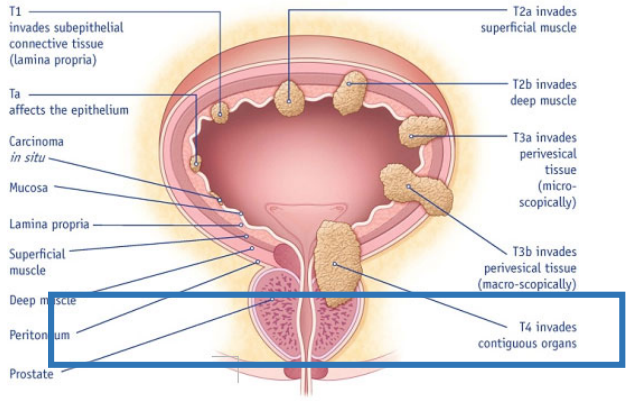


Unfit for Cisplatin
ECOG PS > 2
GFR < 60 mL/min
>gr 2 απώλεια ακοής
>gr 2 περιφερική νευροπάθεια
NYHA III καρδιακή ανεπάρκεια

BSC=best supportive care; GC=gemcitabine plus cisplatin; GFR=glomular filtration rate; MVAC=methotrexate, vinblastine, adriamycin plus cisplatin; HD MVAC=high-dose methotrexate, vinblastine, adriamycin plus cisplatin; PS=performance status; PCG=paclitaxel, cisplatin, gemcitabine.

ΧΗΜΕΙΟΘΕΡΑΠΕΙΑ

- Ενδοκυστική έγχυση
- Νεοεπικουρική (Neoadjuvant)
- Επικουρική (Adjuvant)
- Με ΑΚΘ
- **Προχωρημένη/ Μεταστατική νόσος**



c**T4b**N0M0
cTany**N1-3**M0
cTanyNany**M1**

<u>Οστικές μεταστάσεις</u>
zoledronic acid
denosumab

EAU Guidelines 2019

Second-line treatment
independent of the time of progression after first-line treatment

PS 0-1

Progression (independent of the time interval after receiving first-line chemotherapy), adequate renal function

Standard regimens
1 pembrolizumab
2 atezolizumab
3 nivolumab

Or
1 Clinical trial
2 Comb chemotherapy
3 Monotherapies

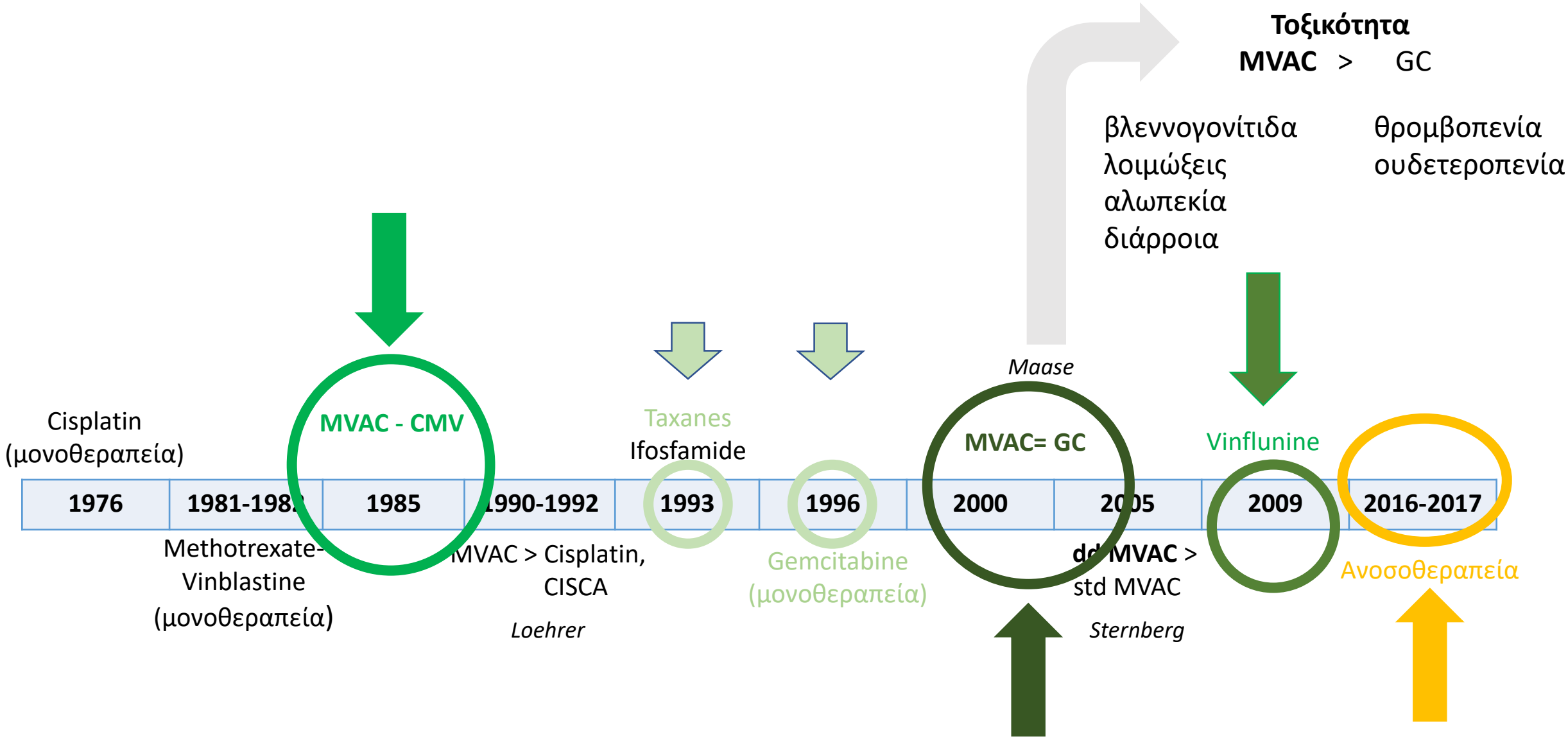
Subsequent treatment
1. Chemotherapy
2. Immunotherapy, if not given as second-line treatment
3. Clinical trial
4. Best supportive care

vinflunine
taxanes

PS ≥ 2

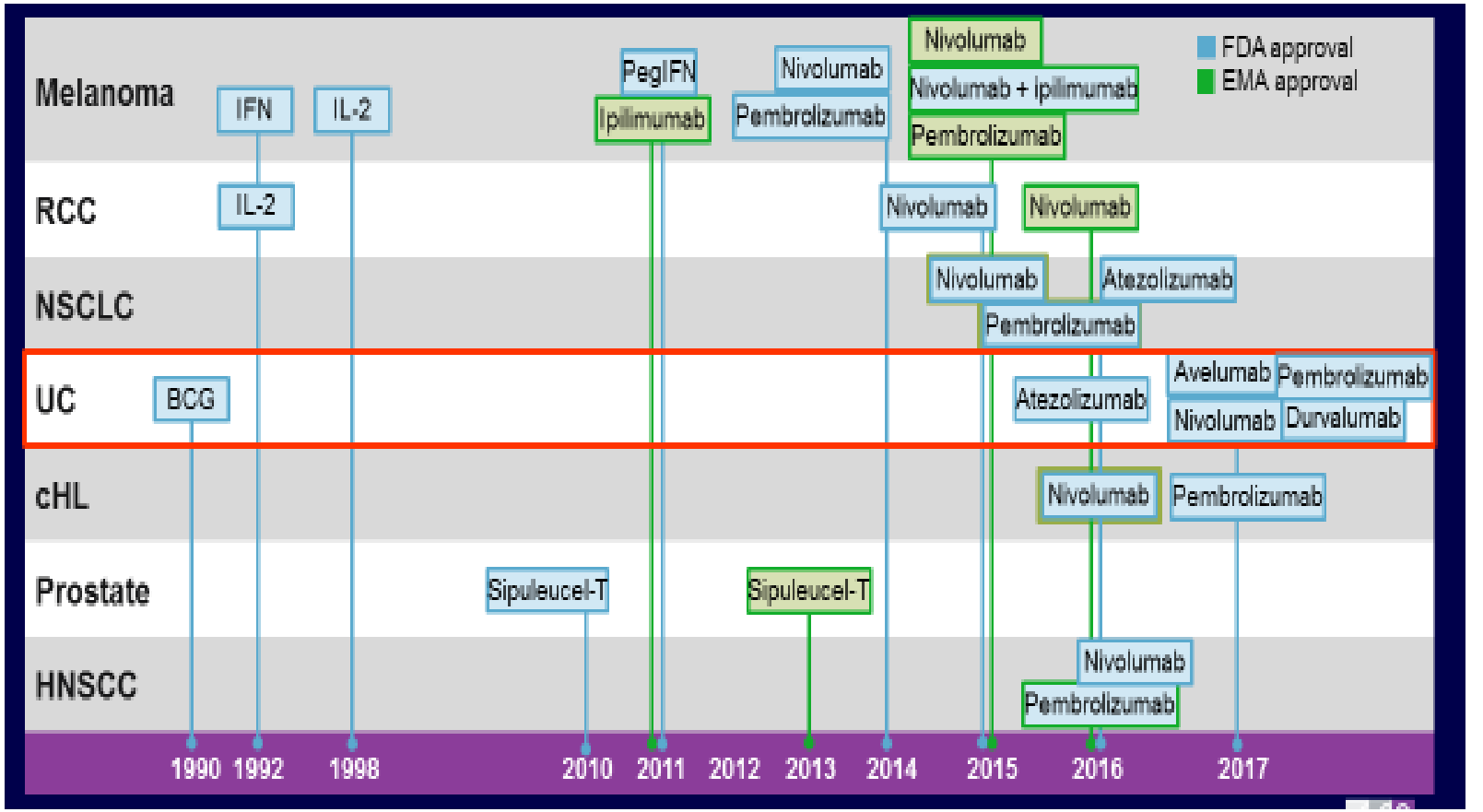
a. Consider immunotherapy
b. Clinical trial
c. Best supportive care

BSC=best supportive care; GC=gemcitabine plus cisplatin; GFR=glomular filtration rate; MVAC=methotrexate, vinblastine, adriamycin plus cisplatin; HD MVAC=high-dose methotrexate, vinblastine, adriamycin plus cisplatin; PS=performance status; PCG=paclitaxel, cisplatin, gemcitabine.



MVAC: Methotrexate, Vinblastine, Doxorubicin, Cisplatin/ CISCA: Cisplatin, Cyclophosphamide, Doxorubicin/ CMV: Cisplatin, Methotrexate, Vinblastine/ GC: Gemcitabine, Cisplatin/ ddMVAC: dose-dense MVAC, stdMVAC: standard MVAC

Immunotherapy Approvals in Urothelial Cancer



NCCN Guidelines Version 1.2019
Bladder Cancer

PRINCIPLES OF SYSTEMIC THERAPY

First-line systemic therapy for locally advanced or metastatic disease (Stage IV)	
Cisplatin eligible	**Preferred regimens** • Gemcitabine and cisplatin[4] (category 1) • DDMVAC with growth factor support (category 1)[2,8]
Cisplatin ineligible	**Preferred regimens** • Gemcitabine and carboplatin[11] • Atezolizumab[12] (only for patients whose tumors express PD-L1[a] or who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 expression) • Pembrolizumab[13] (only for patients whose tumors express PD-L1[b] or who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 expression) **Other recommended regimens** • Gemcitabine[14] • Gemcitabine and paclitaxel[15] **Useful under certain circumstances** • Ifosfamide, doxorubicin, and gemcitabine[16] (for patients with good kidney function and good PS)

FDA approved on April 17, 2017

FDA approved on May 18, 2017

- The presence of both non-nodal metastases and ECOG performance score ≥2 strongly predict poor outcome with chemotherapy. Patients without these adverse prognostic factors have the greatest benefit from chemotherapy. The impact of these factors in relation to immune checkpoint inhibition is not fully defined, but they remain poor prognostic indicators in general.
- For most patients, the risks of adding paclitaxel to gemcitabine and cisplatin outweigh the limited benefit seen in the randomized trial.[17]
- A substantial proportion of patients cannot receive cisplatin-based chemotherapy due to renal impairment or other comorbidities.
  - Participation in clinical trials of new or more tolerable therapy is recommended.

[a] Atezolizumab: PD-L1–stained tumor-infiltrating immune cells covering ≥5% of the tumor area.
[b] Pembrolizumab: Combined Positive Score (CPS) ≥10.

PRINCIPLES OF SYSTEMIC THERAPY

FDA approved:

Subsequent systemic therapy for locally advanced or metastatic disease (Stage IV) (post-platinum)[c] Participation in clinical trials of new agents is recommended.	
Preferred regimen Pembrolizumab (category 1)[18] (May 18, 2017)	**Other recommended regimens** • Albumin-bound paclitaxel[26] • Paclitaxel or docetaxel[24] • Gemcitabine[14] • Pemetrexed[25]
Alternative preferred regimens Atezolizumab[19] (May 18, 2016) Nivolumab[20] (Feb 2, 2017) Durvalumab[21] (May 1, 2017) Avelumab[22,23] (May 9, 2017)	**Useful in certain circumstances based on prior medical therapy** • Ifosfamide[27] • Methotrexate • Ifosfamide, doxorubicin, and gemcitabine[16] • Gemcitabine and paclitaxel[15] • Gemcitabine and cisplatin[4] • DDMVAC with growth factor support[2]

Subsequent systemic therapy for locally advanced or metastatic disease (Stage IV) (post-checkpoint inhibitor) Participation in clinical trials of new agents is recommended.	
Preferred regimen for cisplatin ineligible, chemotherapy naïve • Gemcitabine/carboplatin	**Other recommended regimens** • Albumin-bound paclitaxel[26] • Paclitaxel or docetaxel[24] • Gemcitabine[14] • Pemetrexed[25]
Preferred regimens for cisplatin eligible, chemotherapy naïve • Gemcitabine and cisplatin[4] • DDMVAC with growth factor support[2]	**Useful in certain circumstances based on prior medical therapy** • Ifosfamide[27] • Methotrexate • Ifosfamide, doxorubicin, and gemcitabine[16] • Gemcitabine and paclitaxel[15]

Checkpoint Inhibitors in Platinum-Refractory TCC

	Atezolizumab[1]	Nivolumab[2]	Pembrolizumab[3]	Avelumab[4]	Durvalumab[5]
Phase	Phase II single arm	Phase II single arm	Phase III randomized trial	Phase Ib	Phase I/II
Number of Patients	310	265	270	241 (153 pts ≥ 6 mos f/u)	191 (103 eligible for efficacy analysis)
Dosing	1200 mg every 3 weeks	3 mg/kg every 2 weeks	200 mg every 3 weeks	10mg/kg every 2 weeks	10mg/kg every 2 weeks
ORR	**15%**	**19.6%**	**21.1%**	**17.6%**	**20.4%**
Duration of Response	84% of responses ongoing at median follow-up of 11.7 months	77% of responses ongoing at median follow-up of 7 months	72% of responses ongoing at median follow-up of 14.1 months	89% of responses ongoing at median follow-up of 7.3 months	81% of responses lasting ≥6 months
Median OS	7.9 months	8.7 months	10.3 months	Not reached	14.1 months
Median PFS	2.1 months	2.0 months	2.1 months	1.5 months	2.2 months
Rate of grade 3/4 treatment-related adverse events (AEs)	16%	18%	13.5% (15% grade 3-5)	7.5%	6.8%

1. Rosenberg JE, et al. *Lancet*. 2016;387(10031):1909-1920. 2. Sharma P, et al. *Lancet Oncology*. 2017;18(3):312-322. 3. Bellmunt J, et al. *N Engl J Med*. 2017;376(11):1015-1026. 4. Patel MR, et al. *J Clin Oncol*. 2017;35(Suppl 6S): Abstract 330. 5. Powles T, et al. *J Clin Oncol*. 2017;35(Suppl 6S): Abstract 286.

συμπεράσματα

- **Μη Μυοδιηθητική νόσος** : πλήρης διουρηθρική εκτομή όγκου (TURBT) και άμεση ενδοκυστική έγχυση [χημειοθεραπεία για low-grade Ta, BCG για high-grade Ta και T1 tumors (low- and high-grade)]

- **Μυοδιηθητική νόσος**: **cisplatin-based** neoadjuvant chemotherapy (DDMVAC, GC), σε >T2 νόσο
  cisplatin-based adjuvant chemotherapy ((DDMVAC, GC, CMV) σε T3-T4, N+ νόσος
  θεραπεία διατήρησης της κύστης υπό προϋποθέσεις

- **Προχωρημένη/Μεταστατική νόσος**:

  1ης γραμμής ΧΜΘ: **Gemcitabine and cisplatin** / **DDMVAC**
  αν unfit για cisplatin: carboplatin- ή taxane- based regimens ή μονοθεραπεία ή ανοσοθεραπεία
  2ης γραμμής ΧΜΘ: ανοσοθεραπεία, vinflunine, taxanes, κλινική μελέτη,
  μονοθεραπεία (Cisplatin, Carboplatin, Doxorubicin, 5FU, Ifosfamide, Pemetrexed, Methotrexate και Vinblastine)
  συνδυαστική χημειοθεραπεία με συνδυασμούς των ανωτέρω φαρμάκων

Prognosis depends more on **patients characteristics** and less on agents administered

Σχήματα χημειοθεραπείας

- **std MVAC**: Methotrexate 30 mg/m² iv, days 1, 15, 22
  Vinblastine 3 mg/m² iv, days 1, 15, 22
  Doxorubicin 30 mg/m² iv, day 2
  Cisplatin 70 mg/m² iv, day 2
  every 28d
- **GemCis**: Gemcitabine 1000 mg/m² iv, d1,8,15
  Cisplatin 70 mg/m² iv, d2
  every 28d
- **GemCis**: Gemcitabine 1000 mg/m² iv, d1,8
  Cisplatin 70 mg/m² iv, d2
  every 21d
- CMV: Cisplatin 70 mg/m² iv, d2
  Methotrexate 30 mg/m² iv, d1,8
  Vinblastine 4 mg/m² iv, d1,8
  every 28d
- PAC (ή CISCA): Cisplatin 100 mg/m² iv, d2
  Cyclophosphamide 650 mg/m² iv, d1
  Doxorubicin 50 mg/m² iv,d1
  every 28d
- GemCarbo: Gemcitabine 1,000mg/m² iv, d1,8
  Carboplatin 5AUC, d1
  every 21d
- GemPacl: Gemcitabine 2500 mg/m² iv, d1
  Paclitaxel 150 mg/m² iv, d1

every 14d

- Paclitaxel 80 mg/m² iv, weekly or Docetaxel 100mg /m² iv, d1 every 21d

Ανοσοθεραπεία

Pembrolizumab: 200 mg q3w
Nivolumab: 240mg q2w
Atezolizumab: 1200mg q3w
Avelumab: 10mg/kg q2w
Durvalumab: 10mg/kg q2w

Εντατικοποιημένα σχήματα

- **ddMVAC**: Methotrexate 30 mg/m² iv, day 1
  Vinblastine 3 mg/m² iv, day 1
  Doxorubicin 30 mg/m² iv, day 1
  Cisplatin 70 mg/m² iv, day 1
  every 14d + GCSF
- **ddGemCis**: Gemcitabine 2500 mg/m² iv, d1
  Cisplatin 70 mg/m2
  every 14d +GCSF

Ακτινοευαισθητοποιός ΧΜΘ

Cisplatin + 5-FU	Days 1, 2, 3, 15, 16, and 17: IV hydration at a rate of 500mL/hour; followed by 5-FU 400mg/m² IV push; followed by cisplatin 15mg/m²IV over 1 hour as induction and consolidation therapy.
Cisplatin +paclitaxel	Days 1, 8, and 15: Paclitaxel 50mg/m² Day 1–3, 8–10, 15–17: Cisplatin 15mg/m²; followed by twice-daily radiotherapy for 8 days.
5-FU + mitomycin	Day 1 of radiotherapy: Mitomycin 12mg/m² IV bolus, plus Week 1 (fractions 1–5) and Week 4 (fractions 16–20) of radiotherapy: 5-FU 500mg/m² continuous IV infusion (10 days total).
Cisplatin alone	Cisplatin 100mg/m² IV every 2 weeks for 3 cycles.

Βιβλιογραφία

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ΧημειοΑκτινοθεραπεία

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